REMARKS

Upon entry of the present amendment, claims 1, 16 and 17 will be amended and claim 34 will be added so that claims 1-7, 9-13, and 16-34 will be pending in the application with claim 1 being the sole independent claim. Of the pending claims, claims 1-7, 9-13, 16-32 and 34 are under consideration and claim 33 has been withdrawn from consideration as being directed to a non-elected invention.

Claim 1 has been amended herein in accordance with telephone interviews wherein the Examiner suggested that "blood retentive lipid derivative" be amended to "blood retentive lipid". Moreover, claim 1 has been amended to direct the presently claimed subject matter to be directed to the advantageous amount of the substance for binding the anti-MT-MMP to the lipid membrane structure between 5 and 10 mol% based on the blood retentive lipid in the lipid membrane structure. As discussed with the Examiner, support therefore is present in Applicants' originally filed application, including Tables 5, 6 and 7.

Claim 34 has been added to recite blood retentive lipid in accordance with Applicants' originally filed disclosure, such as at page 10, first full paragraph.

Applicants note that the Examiner has suggested language to remove the word derivative with respect to the blood retentive lipid as being unnecessary. However, the Examiner has not requested changes with respect to the use of "derivative" in other places in the claims. In this regard, Applicants agree that one having ordinary skill would understand the scope and content of the claims. In this regard, as discussed with the Examiner, if any amendments are deemed to be beneficial by the Examiner, the Examiner is requested to contact the undersigned by telephone to discuss the same.

Reconsideration of the rejections and allowance of the application in view of the following remarks are respectfully requested.

Statement of Interviews

Applicants express appreciation for the courtesies extended to Applicants' representatives during an August 7, 2009 telephone interview between Examiner Mark Halvorson and Applicants' representative Sean Myers-Payne; an October 5, 2009 personal interview between Examiner Mark Halvorson and Applicants' representatives Arnold Turk and Mariko Matsukawa; a November 23, 2009 telephone interview between Examiner Mark Halvorson and Examiner Misook Yu and Applicants' representative Arnold Turk; a June 3, 2010 telephone interview between Examiner Mark Halvorson and Examiner Misook Yu and Applicants' representative Arnold Turk; followed by a June 16, 2010 telephone call between Examiner Mark Halvorson and Applicants' representative Arnold Turk.

During the August 7, 2009 interview, the rejections of record were discussed with Applicants' representative presenting arguments that disclosure of 0.5, 1, 5, 10, and 20 mol% supports claims reciting between 0.5 and 20 mol%. The Examiner agreed that this argument appeared to be persuasive, but the Examiner indicated that he would further review the disclosure to ensure support for the claimed range.

Regarding the prior art rejections, Applicants' representative pointed out that calculations in the rejections based upon Zalipsky et al. were incorrect, and that Table 1 of Zalipsky et al. more accurately discloses concentrations of 20, 33, 20, 33, and 20 mol% (from top to bottom). The Examiner indicated that the range was still close to that

recited by Applicants and suggested that a showing of unexpected results might advance prosecution, and was open to further discussion.

During the October 5, 2009 interview, the art based rejections were discussed with Applicants' representative discussing the documents used in the rejections relative to the various features recited in Applicants' claims. The background of Applicants' invention disclosed in Applicants' specification was discussed and contrasted with respect to the disclosures of Bednarski, Kitagawa and Zalipsky. It was submitted that while Bednarski discloses stabilized lipid constructs comprising a liposome, and discloses various agents, there is no teaching or suggestion to arrive at Applicants' claimed subject matter that includes anti-membrane-type matrix metalloproteinase monoclonal antibody (anti-MT-MMP). Unexpected advantages associated with Applicants' claimed subject matter were also referenced with respect to Applicants' specification at the top of page 4.

During the November 23, 2009 interview, the art based rejections were further discussed and no commitment was reached.

During the June 3, 2010 telephone interview, Applicants' claims were briefly contrasted with the prior art used in the rejections. Moreover, Applicants' representative referred the Examiners to Tables 5, 6 and 7 in Applicants' specification as well as the disclosure relating thereto. The Examiners appeared to agree that these showings in the originally filed specification establish patentability of claims directed to between 5 and 10 mol% based on the blood retentive lipid derivative.

During the June 16, 2010 telephone conversation, the Examiner indicated that "blood retentive lipid derivative" should preferably be recited as "blood retentive lipid".

Information Disclosure Statement

Applicants are submitting on even date herewith a Supplemental Information Disclosure Statement. The Examiner is requested to consider the Supplemental Information Disclosure Statement including all documents cited therein, and to confirm such consideration by including a copy of the initialed Form PTO-1449 with the next communication from the Patent and Trademark Office.

Restriction Requirement

Claims 1-7, 9-13 and 16-32 stand elected and examined, and claim 33 is withdrawn from consideration as being directed to a non-elected invention.

Applicants note that newly-added claim is examinable with the elected subject matter, and examination thereof is requested.

Non-elected claim 33 is being permitted to remain pending subject to possible rejoinder upon allowance of the elected claims.

Response to Rejection Under 35 U.S.C. 112, First Paragraph

Claims 1-7, 9-13 and 16-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The rejection contends that there is no support in the specification as originally filed for the recitation of "herein the amount of the substance for binding the anti-MT-MMP to the lipid membrane structure is between 0.5 and 20 mol% based on the blood retentive lipid derivative in the lipid membrane structure." The rejection notes that the specification (Table 2) only discloses DSPE-PEG mal/DSPE-PEG(%) values of 0.5, 1, 5, 10, and 20 mol%.

Initially, Applicants note that claim 1 has been amended to recite "wherein the amount of the substance for binding the anti-MT-MMP to the lipid membrane structure is between 5 and 10 mol% based on the blood retentive lipid in the lipid membrane structure." Moreover, during the June 3, 2010 interview, the Examiner indicated that this amended language is acceptable and supported by Applicants' originally filed application. Accordingly, the rejection of record is moot.

However, Applicants submit that the claims have not been amended based upon this rejection, and the amendment of the claims herein should not be considered to state any agreement and/or acquiescence with the rejection of record. The claims have been amended to advance prosecution of the application by being directed to advantageous embodiments, and Applicants preserve their right to file one or more continuation and/or divisional applications directed to the deleted subject matter. For example, the rejection is without appropriate basis because Applicants submit that disclosure of working examples of 0.5, 1, 5, 10, and 20 mol% provides sufficient written description for the claim recitation of "between 0.5 and 20 mol%." The Examiner is reminded that case law supports that disclosure of values can support ranges for those values. Moreover, *ipsis verbis* support is not required in the application, as is clearly stated in the Patent Office guidelines (see MPEP 2163) and numerous Federal Circuit cases.

Applicants respectfully request withdrawal of the rejection.

Response to Claim Rejections Under 35 U.S.C. 103

The following rejections are set forth in the Final Office Action.

(a) Claims 1-16, 18, 19, 21, 22 and 24-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 2002/0197210 A1 to Bednarski et al. (hereinafter "Bednarski") in view of The Journal of Urology, Vol. 160(4), 1998, pages 1540-1545 to Kitigawa et al. (hereinafter "Kitigawa") in further view of U.S. Patent No.7,108,863 to Zalipsky et al. (hereinafter "Zalipsky").

(b) Claims 1 and 18-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bednarski in view of Kitigawa in further view of U.S. Patent No. 6,417,326 to Cullis et al. (hereinafter "Cullis") and Zalipsky.

(c) Claims 1 and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bednarski in view of Kitigawa in further view of U.S. Patent No. 6,355,268 to Slater et al. (hereinafter "Slater") and Zalipsky

As will be discussed below, during the June 3, 2010 interview, the Examiners appeared to agree that amendment of claim 1 to recite "wherein the amount of the substance for binding the anti-MT-MMP to the lipid membrane structure is between 5 and 10 mol% based on the blood retentive lipid in the lipid membrane structure" is allowable over the prior art of record. Accordingly, in an attempt to advance prosecution of the application, and without expressing any agreement and/or acquiescence with the rejections of record, the claims have been amended to include this apparently allowable subject matter. Applicants again note that they preserve their right to file one or more continuation and/or divisional applications directed to the deleted subject matter including the deleted subject matter, and to present arguments for patentability therein.

Regarding the merits of the rejections, Applicants initially note that the rejections admit that:

> Bednarski et al does not disclose a monoclonal antibody consists of one or more kinds of monoclonal antibodies selected from an anti-Mu -MMP monoclonal antibody, an anti-MT2-MMP monoclonal antibody, an anti-MT3-MMP monoclonal antibody, an anti-MT4-MMP monoclonal antibody, an anti-MT5-MMP monoclonal antibody, and an anti-MT6-MMP monoclonal antibody that that targets tumor cells including urinary tract epithelial cancer and reacts with membrane-type matrix metalloproteinase of a neoplastic vessel, wherein the tumor cell is a cell of fibrosarcoma, squamous carcinoma, neuroblastoma, breast carcinoma, gastric cancer, hepatoma, bladder cancer, thyroid tumor, urinary tract epithelial cancer, glioblastoma, acute myeloid leukemia, pancreatic duct cancer or prostate cancer, which reacts with a membrane-type matrix metalloproteinase of a neoplastic vessel

In fact, a review of Bednarski reveals that Bednarski only appears to disclose the targeting entity being the matrix metalloproteases including MMP2 and MMP9 in claim 15. There does not appear to be any other disclosure in Bednarski relating to the matrix metalloproteases including MMP2 and MMP9 other than claim 15. **In fact, Bednarski's disclosure includes disclosure of a vast number of entities, and there is no motivation to pick and choose the metalloproteases from the vast number of disclosed entities.**

Moreover, a review of claim 15 of Bednarski shows that it is merely directed to a combination of claims 1, 14 and 15 for a combined disclosure of - A stabilized lipid construct comprising a liposome or polymerized vesicle, a targeting entity, a therapeutic entity, and a stabilizing entity; the targeting entity is an antibody; and the antibody has a target selected from the group consisting of P-selectin, E-selectin, pleiotropin, G-protein coupled receptors, endosialin, endoglin, VEGF receptors, PDGF receptor, EGF receptor, FGF receptors, the matrix metalloproteases including MMP2 and MMP9, and prostate

specific membrane antigen (PSMA). Certainly, this does not teach or suggest Applicants' independent claim 1 which is directed to a lipid membrane structure containing an anti-membrane-type matrix metalloproteinase monoclonal antibody (anti-MT-MMP), wherein the lipid membrane structure contains a substance for binding the anti-MT-MMP to the lipid membrane structure and a blood retentive lipid, and wherein the amount of the substance for binding the anti-MT-MMP to the lipid membrane structure is between 5 and 10 mol% based on the blood retentive lipid in the lipid membrane structure.

Thus, while Bednarski discloses stabilized lipid constructs comprising a liposome, and discloses various agents, there is no teaching or suggestion to arrive at Applicants' claimed subject matter that includes anti-membrane-type matrix metalloproteinase monoclonal antibody (anti-MT-MMP).

The rejections try to overcome the deficiencies of Bednarski by relying upon Kitagawa. In particular, the rejections contend that:

> Kitagawa et al discloses an anti-MTI -MMP monoclonal antibody which bound MTI-.MMP on tissue specimens of urothelial carcinoma cells. (page 4, 1st paragraph; page 5, 2nd paragraph, Figure 5). The tissue specimens would include neoplastic vessels.
>
> One of ordinary skill in the art would apply Kitagawa et al's monoclonal antibody to MT1-MMP to Bednarski et al's therapeutic agent comprising an immunoliposome because Bednarski et al claims target entities such as the matrix metalloproteases which include the specie MT1-MMP. Furthermore Kitagawa et al disclose that MT1-MMP is expressed on carcinoma cells which would make MT1-MMP a suitable target for Bednarski et als' immunoliposme. It would have been prima facie obvious to combine Bednarski et al's therapeutic agent comprising an immunoliposome with Kitagawa et al's monoclonal antibody to MT1-MMP to make an immunoliposme that recognized MTI-MMP to target urothelial carcinoma cells expressing MTI-MMP.

In contrast to the assertions in the rejections, Kitagawa does not overcome the deficiencies of Bednarski. Kitigawa is a research paper merely directed to examining the mRNA expression of MT-MMP's and the tissue immunolocalization of MT1-MMP in human urothelial carcinomas. The research of Kitagawa merely concludes that it is possible that MT1-MMP and MT2-MMP play an important role in the invasiveness of human urothelial carcinomas and become candidate tumor markers and targets for anticancer and gene therapeutics. There is no disclosure in Kitigawa that provides enablement and/or written description of any real world use, such as a use having unexpected characteristics as disclosed by Applicants.

In this regard, attention is directed to Applicants' unexpected advantages disclosed beginning in Applicants' originally filed specification at the top of page 4, wherein it is disclosed that:

> The inventors of the present invention also found that the aforementioned lipid membrane structure successfully delivered a medicinally active ingredient and/or a gene also efficiently to an angiogenesis front in the inside of tumor. Specifically, the lipid membrane structure of the present invention can simultaneously target tumor cells and neoplastic vessels, in which MT-MMP is expressed, and can deliver a medicinally active ingredient and/or a gene efficiently to both of them. Conventional lipid membrane structures target either tumor cells or neoplastic vessels. Thus, the lipid membrane structure that can simultaneously target both of tumor cells and neoplastic vessels was first achieved by the present invention. By applying conventional techniques, only a solid tumor grown to some extent can be targeted. In contrast, by the lipid membrane structure of the present invention, a medicinally active ingredient and/or a gene can be delivered to a tumor tissue even in a small stage in which generation of neoplastic vessels is being started, thereby a therapeutic treatment can be attained. The present invention was achieved on the basis of these findings.

Accordingly, there is no teaching or suggestion to arrive at Applicants' claimed subject matter let alone the advantageous results associated therewith, especially when

there is no direction in the prior art to combine the disclosures of Bednarski and Kitigawa in the manner set forth in the rejections of record.

The Examiner is reminded that there must be some teaching or suggestion in the prior art that would motivate somebody having ordinary skill in the art to pick and choose a certain species from a vast disclosure. Moreover, there must be some teaching or suggestion in the prior art that would lead one having ordinary skill in the art to modify the selected species to arrive at Applicants' recited subject matter. In the instant situation, the prior art does not provide any reason why one having ordinary skill in the art would have chosen the matrix metalloproteases including MMP2 and MMP9 in claim 15 of Bednarski. Moreover, the prior art does not provide any sufficient reason to modify such disclosure with anti-MT-MMP.

Still further, the rejections recognize the deficiency of any combination of Bednarski and Kitigawa, and try to address this further deficiency. In particular, the rejections state:

> Further, neither Bednarski et al nor Kitagawa et al disclose that the amount of the substance for binding the anti-MT-MMP to the lipid membrane structure is between 0.5 and 20 mol% based on the blood retentive lipid derivative in the lipid membrane structure.
>
> Zaplipsky et at disclose a DSPE-PEG-mal to DSPE-PEG of 0.5 % while optimizing the cytotoxitiy of immunoliposomes to CDI9+ cells. (Table 1). One of ordinary skill in the art would have been motivated to apply Zaplipsky et al's ratio of DSPE-PEG-mal to DSPE-PEG to Bednarski et al and Kitagawa et al's immunoliposme that recognized MT1 -MMP to optimize the delivery of the immunoliposome to the target urothelial carcinoma cells. It would have been prima facie obvious to combine Bednarski et at and Kitagawa et al's immunoliposme to Zaplipsky et al's ratio of DSPE-PEG-mal to DSPE-PEG to optimize delivery of immunoliposmes that recognized MTI-MMP to maximize cytotoxicity towards urothelial carcinoma cells.

Regarding Zalipsky, Applicants respectfully disagree that Zalipsky et al. discloses the amount of the substance for binding the anti-MT-MMP to the lipid membrane structure of 0.5 mol% based on the blood retentive lipid derivative in the membrane structure. In particular, it appears the Office has misread the cited art. Applicants note that Table 1 of Zalipsky would appear to disclose liposomes having 20, 33, 20, 33, and 20 mol% (from top to bottom in the Table) Mal-lipid based on the blood retentive lipid. Both DSPE-PEG and DSPE-PEG-Mal act as blood retentive lipids and are small components of the lipid composition as a whole in the lipid membrane structure, and DSPE-PEG-Mal also acts as a substance for binding the anti-MT-MMP. Thus, the percentage according to Applicants' claims is based on the percentage of the substance for binding the anti-MT-MMP to the lipid membrane structure to the blood retentive lipid in the membrane structure. One representative example of this, such as in Applicants' Table 2, is DSPE-PEG-Mal to DSPE-PEG plus DSPE-PEG-Mal.

Accordingly, even if for the sake of argument, the disclosure of Bednarski, Kitigawa and Zalipsky were combined Applicants' claimed subject matter would not be at hand.

Cullis and Slater do not overcome any of these deficiencies even if combinable with Bednarski, Kitigawa and Zalipsky.

Accordingly, there is no any teaching or suggestion to arrive at Applicants' claimed subject matter let alone the advantageous results associated therewith.

The Examiner is again reminded that there must be some teaching or suggestion the prior art that would motivate somebody having ordinary skill in the art to pick and choose a certain species from a vast disclosure. Moreover, there must be some teaching

or suggestion in the prior art that would lead to modify the selected species to arrive at Applicants' recited subject matter. In the instant situation, the prior art does not only provide no reason why one having ordinary skill in the art would have chosen the matrix metalloproteases including MMP2 and MMP9 in claim 15 of Bednarski, but the prior art does not provide any sufficient reason to modify such disclosure with anti-MT-MMP in the lipid membrane structure recited by Applicants.

For at least the above reasons a prima facie case of obviousness has not been established, and the rejections should be withdrawn. However, even in the event that a prima facie case of obviousness has been established, Applicants' showing of unexpected results in their examples depicted in Tables 5-7 at page 47, 50 and 51 of their originally filed application, respectively, overcome any prima facie case of obviousness.

In this regard and as discussed with the Examiners during the above-noted June 3, 2010 interview, the examples demonstrate advantageous results when the amount of the substance for binding the anti-MT-MMP to the lipid membrane structure is between 5 and 10 mol% based on the blood retentive lipid in the lipid membrane structure. In this regard, in the recited range there is achieved an advantageous combination of high medicament activity coupled with absence of aggregation and high blood retentivity. For example, in the exemplary embodiments disclosed in Applicants' specification, the recited range achieve an advantageous combination of (a) high medicament activity as illustrated in Table 5 for a representative example of cytostatic ability using doxorubicin (DOX), (b) absence of the presence of aggregation as illustrated in Table 6, and (c) high *in vitro* blood retentivity as illustrated in Table 7.

Accordingly, the rejections of record should be withdrawn for this additional reason.

CONCLUSION

In view of the foregoing amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejections of record, and allow each of the pending claims.

If any issues yet remain which can be resolved by telephone, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,
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June 24, 2010
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